Prenatal Infection and Neurodevelopmental Disabilities

Prenatal infection and mediators of inflammation are risk factors for **neurodevelopmental** disabilities, such as **cerebral palsy** and **autism**.

General Information	
Broad Focus Area	Neurodevelopment and behavior
Background and Justification	Cerebral palsy and autism are uncommon but serious developmental disabilities that have a dramatic effect on the lives of the affected persons and their families. Exposure to prenatal infection or mediators of inflammation may increase risk of cerebral palsy.[1] Fetal inflammatory response to chorioamnionitis (intrauterine infection) includes increased levels of fetal cytokines; such cytokines can be neurotoxic.[2,3] While few studies of chorioamnionitis and cerebral palsy among children born at term have been done,[4,5] it has been estimated that about 28% of cerebral palsy in preterm infants and 12% of cerebral palsy in term infants may be due to chorioamnionitis.[6] A recent study by Wu et al. observed a four-fold increased risk (adjusted) of cerebral palsy in subjects with diagnosed chorioamnionitis.[7] While there are some data on the relation of viral infections in pregnancy to occurrence of autism, few causal agents have been established—rubella being one.[8] The more general relation of prenatal infection, such as chorioamnionitis, and of exposure to mediators of inflammation, to risk of autism has not been studied. Such studies are overdue because of the role immune abnormalities may play in autism and the increased knowledge of the neurotoxicity of inflammatory cytokines.[9] Although a large portion of autism may be genetically determined, the inherited predisposition may increase susceptibility to infection or inflammatory-induced disease.
Prevalence/ Incidence	Cerebral palsy affects approximately 0.2% of children,[10] and autism affects about 0.3%.[11] Whether the frequency of autism is increasing is controversial, because recent estimates of higher prevalence may be due to inclusion of less severe cases. In term pregnancies, about 1-2 percent are affected by chorioamnionitis; in pregnancies ending in preterm births, the prevalence of such infection is higher.[6]
Economic Impact	While no studies have precisely calculated all of the costs associated with autism, a U.K. report estimates the lifetime custodial costs of autism spectrum disorders in the range of $3-$4 million per child, with societal costs likely to be triple the individual estimate.[12, 13] The lifetime economic costs of cerebral palsy have been estimated at $11.5 billion per annual cohort.[14]

Exposure Measures			Outcome Measures	
Primary/ Maternal	Maternal infection/inflammation: - Infection serology (lymphocytes, antibodies, cytokines/interleukins, inflammatory markers) - Medical history of fever and infection (medicine usage) - Dental exams		***Primary/ Child***	Neurological development
Methods	- Blood samples - Vaginal/cervical cultures - Examination by a medical		Methods	Direct observation by medical professional: fetal ultrasound, neurological exam, autism

	professional - Interview			screening test
Life Stage	Repeated measures 1st through 3rd trimesters and birth		Life Stage	Prenatal through year 7
Primary/ Child	Prenatal infection/inflammation: - Infection serology (lymphocytes, antibodies, cytokines/interleukins, inflammatory markers) - Umbilical cord/placental (antibodies; cytokines)		***Secondary/ Child***	School performance
Methods	- Umbilical cord blood culture/pathology		Methods	School record examination for grades/performance
Life Stage	Birth		Life Stage	Follow-up in year 7
Secondary/ Maternal	Retrospective Medical Record Review			
Methods	Medical and obstetrical history, family history			
Life Stage	Repeated measures 1st through 3rd trimesters and birth			

Important Confounders/Covariates	
Family history	Twin and family studies have suggested a genetic link, which may be shown through family histories, to these disorders. [15]
Mother's medical and obstetrical histories	Particularly in cases without a family history, various obstetric complications are often cited as possible causes for fetal neurodevelopmental disruption and consequent disorders. [1]

Population of Interest		**Estimated Effect that is Detectable**
All children		Assuming 100,000 infants born into the study, with an exposure prevalence of 2%, the smallest detectable relative risk would be, for cerebral palsy, 2.8; and for autism, 2.4.

Other Design Issues	
Cost/Complexity of Data Collection	Retention of index children at least to or beyond the average age of diagnosis for these disorders (e.g., age 6 or 7) will be important to address this hypothesis with sufficient power. Necessity of umbilical cord blood samples or samples taken early in infancy may have a very strong impact as there would need for coordination with medical professionals.
Cost of Sample Analysis	Because the contacts with these patients will essentially fall within the scope of standard of care during the pregnancy, additional cost will be relatively minor and entail simply maintaining the pregnancy and infant/childhood data-base and the tissue sample repositories.

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